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Abstract: We carried out an observational study that analyzed population characteristics, metabolic profiles, potentially interacting pharmacotherapy, and related adverse events in second-generation antipsychotics (SGAs) users of a tertiary care hospital. Within our pharmacoepidemiological database derived from electronic medical records of 82,358 hospitalizations, we identified 1136 hospitalizations contributing 9165 patient-days with exposure to SGA. Blood pressure, blood glucose, lipids, and BMI had been documented in 97.7, 75.7, 24.6, and 77.4% of hospitalizations, respectively. Among these, the prevalence of hypertension, hyperglycemia, dyslipidemia, and BMI 30 kg/m or more was 36.9, 22.6, 61.1, and 23.1%, respectively. A total of 63.4, 70.8, and 37.1% of SGA users with hyperglycemia, dyslipidemia, and hypertension, respectively, received no pharmacotherapy for these conditions. We identified 614 patient-days with SGA plus formally contraindicated comedication and another 1066 patient-days with other high-risk combinations for QTc prolongation. Among those there was one case with associated neutropenia and four cases with abnormal QTc interval. However, specific monitoring for such adverse events was not documented in 45.5% of hospitalizations with contraindicated and 89.8% with high-risk QTc-prolonging combinations. Our study identified targets for improved monitoring and management in SGA users. These may be implemented as automated alerts into electronic prescribing systems and thereby efficiently support safer pharmacotherapy in clinical practice.

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Introduction

Second-generation antipsychotics (SGAs) are primarily indicated for the treatment of schizophrenic disorders, and some SGA such as quetiapine, risperidone, aripiprazole, and lurasidone also have labeled indications for other psychiatric disorders including bipolar diseases. A pronounced increase in the use of antipsychotics has been observed over the past 20 years, which is mostly attributable to the increased prescription of SGA since their introduction in the mid 1990s (Verdoux *et al.*, 2010; Donohue *et al.*, 2014). Off-label use has also been reported to be very common for SGA in clinical practice – for example, for the treatment of dementia and symptoms of anxiety, sleep, and neurotic disorders (Linden and Thiels, 2001; McKean and Monasterio, 2012).

SGAs are not generally more effective than first-generation antipsychotics (Carpenter and Buchanan, 2008), but they have a distinct profile of adverse effects. Fewer extrapyramidal adverse effects are traded for more metabolic adverse effects including weight gain, hyperglycemia, and dyslipidemia (De Hert *et al.*, 2012a, 2012b). The risk of such metabolic abnormalities appears to vary for different SGA and lowering this risk has been an important goal in the development of more recently approved substances such as aripiprazole, ziprasidone, and lurasidone (American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity, 2004; Leucht *et al.*, 2009). Nevertheless, current drug labels as well as international guidelines recommend that the metabolic profile should be monitored before and during treatment with SGA, particularly in patients with pre-existing metabolic disorders and other cardiovascular risk factors (Mitchell *et al.*, 2012). Therefore, studies on the frequency of metabolic disorders, their management, and the actual implementation of labeled recommendations in SGA users in routine clinical practice are an important contribution for the postmarketing evaluation of the real-life risks and benefits of SGA (Verdoux *et al.*, 2010; Mitchell *et al.*, 2012).

Furthermore, SGA can prolong the QTc interval, with an associated increased risk of ventricular arrhythmia and sudden cardiac death (De Hert *et al.*, 2012a; Weeke *et al.*,

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2014). The risk for cardiac and other adverse drug reactions may be enhanced by clinically relevant drug interactions. Pharmacokinetic interactions may occur with inducers or inhibitors of the CYP450 enzyme system and may alter the plasma concentrations of SGA such as the CYP3A4 substrates clozapine and quetiapine. Pharmacodynamic interactions may also be problematic – for example, when several QT-prolonging drugs are combined. Consequently, a considerable number of drug combinations with SGA are labeled as formally contraindicated and other potentially interacting combinations have labeled warnings requiring that the risk–benefit ratio be carefully assessed and that close monitoring for adverse events must be performed. However, there are limited real-life data on the actual prevalence and clinical relevance of potentially interacting comedication with SGA.

The trend toward increased use of SGA may also be observed in tertiary care hospitals where patient characteristics, indications, and usage patterns are different compared with psychiatric hospitals or outpatient settings. The current study, therefore, had three main aims that we sought to evaluate in the real-life setting of a tertiary care hospital: first, to explore prescribing patterns of SGA, second to analyze how metabolic complications of patients receiving SGA are monitored and managed, and third to analyze the prevalence, monitoring, and clinical relevance of potential drug interactions with SGA.

Methods

We carried out a retrospective observational study that analyzed SGA use and related population characteristics, metabolic profiles, concomitant pharmacotherapy, and adverse events in a tertiary care hospital. The cantonal ethics committee, the hospital's medical director, and the hospital's center for clinical research had approved the data extraction, the setup and analysis of the anonymized pharmacoepidemiological database, and the access to original medical records for our research studies.

Data source

For the current study, we used comprehensive data for the time period from 1 January 2011 to 31 December 2012 from our anonymized pharmacoepidemiological database containing information on demographics, laboratory results, and electronic drug prescriptions for hospitalized patients of a tertiary care hospital. The hospital provides medical care to a population of about 1.5 million individuals and has ~1000 beds and 40 clinical specialty divisions. The database builds on information extracted from the hospital's electronic clinical information system featuring electronic drug prescription (computerized physician order entry). The system records not only prescriptions but also a confirmation for each drug's actual administration (and its time) to the patient. Our analyses included all prescriptions with documented administration from all hospitalized patients during the study period, except patients staying at ICUs, where computerized physician order entry has not yet been introduced. We performed extensive reformatting, quality controls, and matching of Anatomical Therapeutic Chemical Classification System (ATC) codes to ensure identification of all administered drugs and their doses. In addition, we also compiled information on indication for SGA use, metabolic parameters, blood counts, and ECG QTc interval measurements for the population of the current study.

Study population and design

Selection of the study population and the overall study design are presented in Fig. 1. All patients with at least one full calendar-day of hospitalization and a documented administration of SGA were included in the study. The admission and the discharge day of each hospitalization were excluded from our analyses because drug administrations and events are not comprehensively recorded in the available data for those days. We included all SGA from our dataset that were defined as such by the US Federal Drug Administration (FDA, 2014a) and the German Psychiatrist's Association (DGPPN, 2006) – that is, amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Within the resulting study population, we analyzed the following outcomes: (i) SGA usage patterns; (ii) metabolic parameters and their monitoring; and (iii) potential drug–drug interactions including associated adverse events and their monitoring.

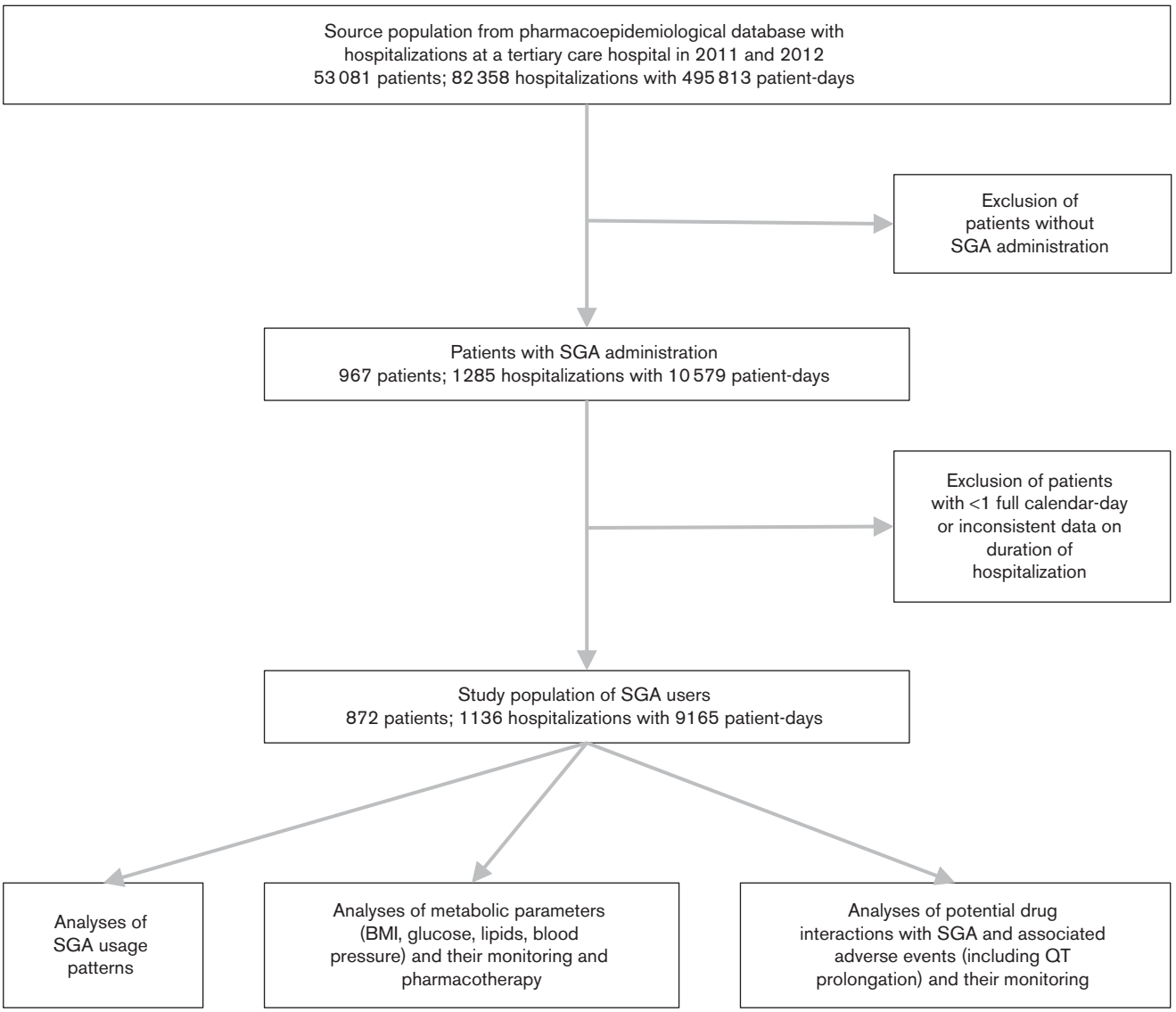
Second-generation antipsychotic usage patterns

SGA use was descriptively analyzed in terms of patient characteristics, primary diagnoses, indications, and prescription frequencies. Indications for SGA use were determined according to all related information found in the electronic medical records and classified into one of the following seven categories: (i) endogenous psychotic disorders (schizophrenia, schizoaffective disorders, other psychotic nonorganic disorders); (ii) exogenous psychotic disorders (substance-induced behavior disorder or delirium, delirium in acute organic psychosis, dementia in chronic organic psychosis); (iii) affective disorders (bipolar disorder with depressive or manic episode, depression); (iv) personality disorder (borderline, emotional instability, other); (v) anxiety disorder and state of anxiety or excitation; (vi) sleeping and eating disorders; and (vii) other indications (hallucination, agitation, somatogenic psychic disorder).

Metabolic parameters and their monitoring

Metabolic abnormalities were defined according to a published joint scientific statement of six international organizations (Alberti *et al.*, 2009) and assessed for each hospitalization. The mean blood pressure was calculated from the first documented measurement on each patient day with SGA exposure for each hospitalization. BMI was

Fig. 1



Study design and selection of the study population. SGA, second-generation antipsychotic.

calculated from the first recorded measurement of height and weight during hospitalization or, if not available, derived from other information on nutritional status in the medical records. For metabolic laboratory values (blood glucose, HbA1c, and blood lipids), all measured values during hospitalization were recorded. We identified treatment with antidiabetic, antihypertensive, and lipid-modifying drugs, and we also recorded treatment with glucocorticoids because these may increase blood glucose and therefore act as confounders.

Potential drug interactions and associated adverse events

We identified potential drug–drug interactions of SGA with all contraindicated drugs that were administered on the same calendar-day. For this purpose, we first established a list of formally contraindicated drugs according to the manufacturers' national drug labels for each SGA (*http://www.swissmedicinfo.ch*). For labeled contraindications that referred to specific drug characteristics (e.g. drugs known to cause QTc prolongation, agranulocytosis, or drug-metabolizing CYP450 enzyme inhibition), we established lists of drugs fulfilling these criteria. These were based on comprehensive available scientific information sources including specialized drug interaction software and websites (CBER-CDER, 2005; AZCERT, 2014; FDA, 2014b; Indiana University, 2014; mediQ-PDAG, 2014). For drug combinations with SGA that were not formally contraindicated, but require careful monitoring of the QTc interval according to the

manufacturers' national drug labels, we established additional lists with the drugs' ATC codes. For all potentially interacting drugs that prolong QTc interval or inhibit CYP450 enzymes, we only included drugs that showed a strong or a moderate effect according to at least one reference. We only analyzed hospitalizations where at least one strong CYP450 inhibitor or at least two moderate CYP450 inhibitors were coadministered at the same patient day. For every hospitalization for which we identified potential interactions with SGA, we validated whether any adverse events known to be associated with those interactions had actually occurred and whether active monitoring for such events had been performed. We reviewed the original medical records for any events and clinical diagnoses that might represent an adverse drug reaction caused by the respective drug interactions. We checked whether ECG was monitored on days on which SGA were coadministered with contraindicated or potentially critically interacting drugs. Monitoring for QTc prolongations was evaluated by reviewing all ECGs of all hospitalizations with QTc-prolonging drug combinations in the medical records. A QTc interval more than 450 ms in men and more than 460 ms in women is associated with increased cardiovascular mortality and defined the upper limit of normal by the American Heart Association and this was accordingly categorized as 'abnormal QTc' for the present study (Rautaharju *et al.*, 2009; Schouten *et al.*, 1991). A QTc interval more than 500 ms significantly increases the risk of torsades de pointes tachycardia and sudden cardiac death (CBER-CDER, 2005; Beach *et al.*, 2013) and was defined as 'long QTc' in our study.

For contraindicated drug combinations with an increased risk of agranulocytosis that had been coadministered for at least 3 consecutive days, we reviewed the results of all available blood counts. Neutropenia was defined as a neutrophil blood count less than 1.4 g/l and agranulocytosis as a count less than 0.5 g/l.

If an associated adverse event was documented, three investigators with special expertise in pharmacovigilance and formal causality assessment (S.R., D.F.N., and C.G.) assessed the causal relationship of the adverse event with the interacting drug combination using internationally standardized WHO/CIOMS causality assessment criteria (WHO-UMC, 2012).

Data analysis

Data analysis is descriptive, with presentation of results in tables as appropriate. Frequencies were calculated for individual patients, hospitalizations, and patient-days. Data management and analyses were carried out using STATA (version 13.1; STATA Corporation, College Station, Texas, USA).

Results

The source population included 53 081 individual hospitalized patients contributing 82 358 hospitalizations and 495 813 patient-days. After exclusion of patients without SGA use and less than at least one full calendar-day of hospitalization, the resulting study population included 872 patients with 1136 hospitalizations and 9165 patient-days. In total, we analyzed the circumstances of 14214 single SGA administrations (Fig. 1).

Second-generation antipsychotic usage patterns

The characteristics of the study population are presented in Table 1. Women accounted for SGA use in 50.9% of the hospitalizations and 60.1% of the patient-days. The mean and the median duration of hospitalization for all

Table 1 Characteristics of the study population of second-generation antipsychotic users in a tertiary care hospital

Characteristics	Hospitalizations [*n* (%)]	Patient-days [*n* (%)]
All analyzed SGA users	1136 (100)	9165 (100)
Sex		
Female	578 (50.9)	5506 (60.1)
Male	558 (49.1)	3659 (39.9)
Age (years)		
< 18	8 (0.7)	131 (1.4)
18–44	280 (24.6)	3119 (34.0)
45–64	430 (37.9)	2787 (30.4)
65–84	357 (31.4)	2766 (30.2)
≥ 85	61 (5.4)	362 (3.9)
Use of different SGA[a]		
Quetiapine	599 (52.7)	4276 (46.7)
Olanzapine	234 (20.6)	2543 (27.9)
Risperidone	170 (15.0)	1214 (13.7)
Clozapine	115 (10.1)	866 (9.4)
Aripiprazol	51 (4.5)	379 (4.1)
Amisulpride	22 (1.9)	102 (1.1)
Paliperidone	13 (1.1)	49 (0.6)
Ziprasidone	1 (0.1)	11 (0.1)
Units with highest use of SGA[b,c]		
Neurology	167 (14.7)	1325 (14.5)
Trauma surgery	134 (11.8)	900 (9.8)
Internal medicine	92 (8.1)	873 (9.5)
Neurochirurgy	66 (5.8)	455 (5.0)
Plastic surgery	66 (5.8)	457 (5.0)
Psychiatry–psychotherapy	37 (3.3)	1772 (19.3)
Documented indications for SGA use[d]		
Affective disorders	287 (31.9)	1897 (24.3)
Endogenous psychotic disorders	224 (24.9)	1439 (18.5)
Exogenous psychotic disorders	176 (19.6)	1278 (16.4)
Sleeping disorders and eating disorders	84 (9.3)	2110 (27.1)
Anxiety disorders	57 (6.3)	593 (7.6)
Other	48 (5.3)	361 (4.6)
Personality disorders	23 (2.6)	115 (1.5)
No indication documented[e]	237 (20.9)	1372 (15)

SGA, second-generation antipsychotic.
[a]Total of hospitalizations/patient-days exceeds the number of analyzed hospitalizations/patient-days because of the use of multiple SGA on some patient-days. The total of % therefore exceeds 100.
[b]Percentage of hospitalizations: hospitalizations of all analyzed cases with the use of SGA (1136 hospitalizations).
[c]Percentage of patient-days: prevalence of patient-days on these wards with the use of any SGA in 2011 and 2012.
[d]Percentage of hospitalizations where indication was available (899 hospitalizations).
[e]Percentage of hospitalizations with no indication of all hospitalizations (1136)/percentage of patient-days with no indication of all patient-days (9165).

patients on SGA was 14 and 7 days, respectively. Quetiapine was the most frequently used SGA in the population studied (46.7% of all patient-days with SGA exposure), followed by olanzapine (27.9%) and risperidone (13.7%). The three most frequently coadministered drug groups with SGA were analgesics (ATC class N02, 8210 patient-days, 10.0% of all coadministered drugs), antithrombotic agents (ATC class B01, 7485 patient-days, 9.2%), and so-called psychoanaleptics, a group within the ATC classification that comprises antidepressants, psychostimulants, nootropics (=cognitive enhancers), antidementia drugs, and combinations with psycholeptics (ATC class N06, 6027 patient-days, 7.1%). The small unit of psychiatry and psychotherapy (accounting for only 2.2% of all patient-days in the source population) expectedly had the highest prevalence of SGA use (on 23.8% of the patient-days in the unit) and accounted for 19.3% of all patient-days with SGA exposure in the hospital. The remaining 80.6% of SGA use occurred in nonpsychiatric units. In the neurology unit, SGA were used on 6.5% of the patient-days, representing 14.5% of all SGA use at the hospital. Besides the psychiatry and neurology units, we found the highest prevalence of SGA exposure in the units of plastic surgery and infectious diseases (on 4.2 and 4.0%, respectively, of all patient-days in these units). Because of their large absolute number of hospitalizations, trauma surgery and internal medicine were also major contributors to SGA use in the population studied (9.8 and 9.5%, respectively, of all patient-days with SGA exposure in the hospital). Indications for SGA prescriptions were identifiable in 899 hospitalizations and are also presented in Table 1. Affective disorders (31.9%), endogenous psychotic disorders (24.9%), and exogenous psychotic disorders (19.6%) were the three most frequently documented indications for SGA. The most common primary diagnoses of patients receiving SGA during hospitalization according to their documented ICD-10 codes were cerebrovascular disorders (ICD codes I60–I69, 4.2%), behavioral disorders with somatic disorders and factors (ICD codes F50–F59, 3.9%), and other forms of heart disease (ICD codes I30–I52, 3.9%). During most hospitalizations, only one SGA was administered per day, but in 5.7% of the analyzed hospitalizations, two SGA were administered simultaneously on at least one patient-day and in 0.2% of the analyzed hospitalizations, three SGA were administered.

Metabolic parameters, their monitoring, and treatment

The monitoring of metabolic parameters in SGA users as well as the prevalence of metabolic disorders among those where monitoring was performed are presented in Table 2. Blood glucose and lipid profiles had not been determined in 24.3% ($n=276$) and 75.4% ($n=856$) of SGA users, respectively. In 58.3% of the cases in which any lab data on any metabolic status were available, we found at least one metabolic abnormality. Furthermore, SGA users with prevalent metabolic disorders received no pharmacotherapy for those conditions in 63.4% of the hospitalizations with hyperglycemia as well as in 70.8 and 37.1% with dyslipidemia and hypertension, respectively. Among all patients on SGA, 244 (28.0%) fulfilled the diagnostic criteria for metabolic syndrome as defined by a consensus group (Alberti *et al.*, 2009). There were no apparent major differences in the prevalence of metabolic abnormalities between users of different SGA.

Potential drug interactions and associated adverse events

The prevalence of combined use of SGA with drugs that are formally contraindicated as well as with drugs that are not formally contraindicated but have a labeled high risk of QTc prolongation in combination with SGA are presented in Table 3.

Coadministration of formally contraindicated drugs with SGA was present on 614 patient-days emerging from 112 hospitalizations. Among these, we identified three cases with clinically relevant adverse events that were related to the respective coadministrations with a 'probable' causal relationship according to the WHO/CIOMS causality criteria: one case with neutropenia and two cases with abnormal QTc. However, in 51 of the 112 hospitalizations, there was no monitoring of blood count or QTc interval; thus, the presence of related adverse events cannot be excluded for these patients. Coadministrations of QT-prolonging combinations that were not formally contraindicated but potentially dangerous were identified in 176 hospitalizations. Among these, ECG monitoring for adverse events was performed in only 18 (10.2%) patients, and among these, we identified two cases with abnormal QTc and a 'probable' causal relationship with the critical combination.

Discussion

The current study analyzed SGA use and associated metabolic profiles and potential drug interactions including their outcomes in a real-life inpatient setting of a tertiary care hospital. We found that 1.6% of all hospitalized patients received SGA, about one third of SGA users were 65 years and older, more than 80% of SGA were prescribed to patients admitted for nonpsychiatric primary diagnoses, and that cerebrovascular disorders and heart disease ranked among the top three primary admission diagnoses. These features characterize SGA users in a tertiary care hospital as a high-risk population for cardiovascular and cerebrovascular events and frequent polypharmacy, the latter predisposing to a high risk for drug interactions (Fritz *et al.*, 2012). Quetiapine and olanzapine accounted for the majority of SGA use, and both are well known to cause metabolic disorders and QT prolongation. The predominant use of quetiapine is also in line with previous reports (Greil *et al.*, 2012; Donohue *et al.*, 2014), and quetiapine is subject to drug interactions

Table 2 Prevalences of metabolic disorders and of their monitoring and pharmacotherapy

	Absolute and relative frequencies
Total number of hospitalizations with SGA use	1136 (100%)
Obesity	
No weight, height, or nutritional status documented	256 (22.6% of total)
BMI based on weight, height, or additional data	880 (77.4% of total)
BMI ≥ 25 kg/m^2	459 (52.1% of those with available BMI)
BMI ≥ 30 kg/m^2 (= obesity)	203 (23.1% of those with available BMI)
Glycemic disorder	
Blood glucose not measured	276 (24.3% of total)
Blood glucose values available	860 (75.7% of total)
Glycemic disorder[a]	194 (22.6% of those with glucose values)
Pharmacotherapy for diabetes	71 (36.6% of those with glycemic disorder)
Glucocorticoids coadministered	36 (18.6% of those with glycemic disorder)
Lipid disorder	
Blood lipids not measured	856 (75.4% of total)
Blood lipid values available	280 (24.6% of total)
Lipid disorder[b]	171 (61.1% of those with lipid values)
Pharmacotherapy for lipid disorder	50 (29.2% of those with lipid disorder)
Hypertension	
Blood pressure not measured	26 (2.3% of total)
Blood pressure values available	1110 (97.7% of total)
Hypertension[c]	410 (36.9% of those with blood pressure values)
Pharmacotherapy for hypertension	258 (62.9% of those with hypertension)

Criteria for metabolic disorders were defined according to published consensus guidelines (Alberti *et al.*, 2009).
SGA, second-generation antipsychotic.
[a]Fasting glucose ≥ 5.6 mmol or spontaneous glucose ≥ 11.1 mmol/l or HbA1c > 5.9% (women) or > 5.7% (men).
[b]Total cholesterol ≥ 5 mmol/l and/or HDL-cholesterol ≤ 1 mmol/l and/or triglycerides ≥ 1.7 mmol/l
[c]Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mm Hg.

with inducers and inhibitors of CYP3A4 drug-metabolizing enzymes. Inducers and inhibitors of CYP450 enzymes are used frequently in tertiary care hospitals including for example several antiepileptic, antifungal, and antibiotic drugs. Aripiprazole, with its presumably lower risk for causing adverse metabolic effects, was not used as frequently, but it is also subject to interactions through CYP2D6 and CYP3A4, and QT prolongation is a well-known associated risk. Clozapine accounted for 10% of SGA use, and bone marrow suppression is a major concern in addition to its associated risk of interactions and QT prolongation. This risk is further increased in combination with other drugs that may cause neutropenia and agranulocytosis such as metamizole, methotrexate, or azathioprine, and requires regular blood count monitoring. Ziprasidone and lurasidone, which are comparable to aripiprazole in that they are also considered to have a low risk of metabolic disorders, were not (yet) marketed in Switzerland during the study period.

Furthermore, documented indications suggest that off-label prescriptions account for a major part of SGA use in the setting studied, particularly for sleeping and eating disorders. This is in accordance with other studies in different populations and confirms the common practice of prescribing SGA beyond their labeled indication (Linden and Thiels, 2001; McKean and Monasterio, 2012). In some cases, off-label use may constitute an avoidable risk and a formal and clinically relevant medication error. However, off-label use as well as the coprescription of potentially interacting drugs does not necessarily have to be problematic, sometimes even for formally contraindicated drug combinations. In many instances, it can be justified if possible risks are thoroughly weighed against benefits and if there are no alternatives and no clear evidence of the clinical relevance of risks. Nevertheless, this practice always implies at least an increased burden of responsibility for the prescribing physician and the hospital where it occurs. Therefore, in all those instances, at least monitoring for adverse events should be taken seriously. From a broader perspective, the growing number of individuals exposed to SGA calls for population studies assessing risks versus benefits of SGA use also for disorders other than psychosis and for unlabeled use (Verdoux *et al.*, 2010).

Our study provides a two-sided answer to these issues. On the one hand, it is reassuring that we identified only five adverse events related to drug interactions with SGA use in our study population over a time of two calendar years, and none of them was irreversible. Given our thorough case-by-case evaluation, we also consider it as unlikely that we missed serious adverse drug reactions caused by interactions with SGA during hospitalization. On the other hand among SGA users with monitoring of the according parameters, we found that the prevalence of hypertension, hyperglycemia, dyslipidemia, and BMI 30 kg/m^2 or more was 36.9, 22.6, 61.1, and 23.1%, respectively, and that of these, 37.1, 63.4, and 70.8%, respectively, received no pharmacotherapy for these conditions. Equally importantly, we also found that a large proportion of SGA users received insufficient monitoring for adverse metabolic effects and QT prolongation. Furthermore, if problematic medication is continued, adverse events occurring after discharge may have remained undetected, particularly arrhythmia associated with QT prolongation and long-term

Table 3 Drug interactions with second-generation antipsychotic including their monitoring and associated adverse events

	Overall use of involved SGA		Use of SGA with contraindicated drug		Use of contraindicated combination without monitoring	Adverse events
Potentially interacting drug combinations	Hospitalizations (*n*)	Patient-days (*n*)	Hospitalizations (*n*)	Patient-days (*n*)	Hospitalizations (*n*)	Case description
Combinations with a labeled contraindication						
Clozapine and drugs that increase the risk of agranulocytosis	114	866	68	349	15	Neutropenia under combined therapy of clozapine with metamizole (neutrophils, 1.01 g/l; normal > 1.4 g/l). Full recovery to normal values after stopping metamizole
Quetiapine and CYP3A4 inhibitors	599	4276	30	182	25	Abnormal QTc (463 ms) under combined therapy of quetiapine with voriconazole. Therapy continued, no follow-up ECG
Amisulpride and drugs with high or moderate potential of QTc prolongation	22	102	13	72	10	One case identified as part of internal quality management, but no documented consent from patient to publish details from original medical records for research purposes
Ziprasidone and drugs with high or moderate potential of QTc prolongation	1	11	1	11	1	No cases with adverse events identified
Combinations with a labeled high risk of QT prolongation without formal contraindication						
Clozapine and drugs with high and moderate potential of QTc prolongation	115	866	58	388	51	Abnormal QTc (477 ms) under combined therapy of clozapine with quetiapine, sertindole, lithium, amitriptyline, and ciprofloxacin. Therapy continued, no follow-up ECG
Risperidone and drugs with high and moderate potential of QTc prolongation	170	1214	111	647	100	Abnormal QTc (487 ms) and symptomatic supraventricular extrasystoles under therapy with risperidone 5 h after intravenous administration of ondansetrone. Normal QTc (435 ms) after stopping ondansetrone
Paliperidone and drugs with high and moderate potential of QTc prolongation	13	49	7	31	7	No cases with adverse events identified

SGA, second-generation antipsychotic.

adverse effects of metabolic disorders (Weeke *et al.*, 2014). Indeed, in our function as a regional pharmacovigilance center, we regularly receive reports of avoidable serious and sometimes fatal adverse drug reactions (particularly torsade de pointes tachycardia) associated with drug interactions with SGA, underlining their clinical relevance. Severe adverse effects of SGA and a need for improved monitoring in clinical practice are also documented in the literature. Girardin *et al.* (2013) reported fatal cases of arrhythmia associated with SGA in their well-designed prospective study and a study in a Swiss psychiatric outpatient setting systematically screened SGA users for dyslipidemia and reported a prevalence of 21–27% (Choong *et al.*, 2012). The low proportion of SGA users who are screened for metabolic abnormalities in the present study is also in line with results from a recent meta-analysis, which found that monitoring of metabolic risks in patients treated with antipsychotic medication is performed routinely in only 69.8% (blood pressure), 44.3% (glucose), 59.9% (triglycerides), and 41.5% (cholesterol) (Mitchell *et al.*, 2012). In the CATIE landmark trial, 89% of patients with dyslipidemia and 45% of patients with diabetes were untreated (Manschreck and Boshes, 2007).

For the interpretation of our findings, one has to consider some limitations imposed by the data source and study design. We followed patients during hospitalization, but for the time before admission and after discharge, we could not collect comprehensive information on the duration of SGA use, metabolic profiles, and adverse events. Therefore, frequencies of metabolic abnormalities must be considered as cross-sectional prevalence data, whereas no conclusions can be drawn on their incidence and causal relationship in relation to SGA use. Another interesting question relates to the comparative risk of metabolic disorders caused by different SGA. We found no apparent differences in the prevalences over different SGA, but such a comparison is subject to uncontrollable indication and diagnostic bias in our retrospective study – that is, one would assume that, for example, aripiprazole might be administered more frequently to patients with pre-existing known metabolic problems and with more frequent monitoring. The interpretation of any such comparisons would therefore be limited and, in the worst case, even be misleading. Furthermore, some patients may have received SGA only for a short time, which may still be relevant for the risk of QT prolongation, but less so in terms of adverse metabolic outcomes. In addition, prevalent metabolic abnormalities do not always equal an indication for pharmacological treatment. Nevertheless and irrespective of these limitations, we must assume that monitoring of the QT interval and/or metabolic parameters, management implications such as glucose-lowering and lipid-lowering pharmacotherapy, or switching to other SGA and avoiding interacting drug combinations would have been indicated in a considerable proportion of SGA users.

From a pragmatic perspective, one must realize that it is a challenging task to achieve changes in the prescribing and monitoring of SGA therapy with the aim of avoiding critical interactions and adverse effects in clinical practice. However, the introduction of electronic medical records with electronic drug prescription provides new opportunities for efficient and effective clinical decision support. Today, we already screen pharmacotherapy for potential medication errors in the electronic medical records at our institution as part of our proactive quality management efforts. We have also started the implementation of semiautomated screening algorithms for specific medication errors into our electronic prescribing system, followed by recommendations on patient management in case of clinical relevance. Implementation of such clinical decision support measures for SGA could help prevent associated adverse effects. Switching to SGA that are less likely to cause metabolic complications in patients with metabolic abnormalities has shown promising results and – if sufficient efficacy can be achieved – should be preferred over adding pharmacological treatment against the metabolic complications, which adds to the patients' drug burden and may compromise their compliance (Mukundan *et al.*, 2010; De Hert *et al.*, 2012b; Tse *et al.*, 2014).

In conclusion, our findings suggest that serious adverse effects of drug interactions with SGA are very rare, but also that a considerable proportion of patients with SGA exposure are neither adequately monitored nor managed, particularly in terms of metabolic risks and QT prolongation. New opportunities through electronic medical records with highly specific electronic clinical decision support may play a key role in proactive safety management of antipsychotic and other pharmacotherapy in the future.

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Conflicts of interest

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